significant morbidity and mortality. Factors likely include pathogenesis of the disease as well as prolonged prior exposure to cytotoxic chemotherapy and immune suppression. Clinical approaches to improve outcomes should optimize disease control while minimizing toxicity before and after transplant.

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IMPROVED SURVIVAL FOLLOWING HLA-MATCHED RELATED MARROW TRANSPLANTATION IN PEDIATRIC PATIENTS WITH SEVERE APLASTIC ANEMIA: (A 39-YEAR RETROSPECTIVE ANALYSIS)

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Allogeneic marrow transplantation offers curative therapy for pediatric patients with severe aplastic anemia. Over the past 4 decades, significant improvements in the long term outcome of patients treated with allogeneic marrow grafts have resulted from progress in the prevention and treatment of graft rejection and graft-versus-host disease (GVHD). Here we report the outcome of 149 pediatric patients, ages 2-19 years who received HLA-matched related marrow grafts for treatment of severe aplastic anemia between 1971 and 2009. Patients were divided into 3 groups, reflecting changes in conditioning and GVHD prophylaxis regimens that occurred over time. Group 1 consisted of 100 patients who were conditioned with Cyclophosphamide (CY; 200 mg/kg) followed by "long" (102 days) Methotrexate (MTX) for GVHD prevention. Group 2 consisted of 19 patients who received CY followed by "short" (days 1, 3, 6, and 11) MTX and cyclosporine (CSP; through day 180). Group 3 consisted of 30 patients who were conditioned with CY and horse antithymocyte globulin (ATG) followed by MTX and CSP for GVHD prevention. The risk of mortality was significantly different between the 3 groups ($p < 0.0001$). With a median follow up of 25.2 (range, 0.3-37) years, the 5-year survival estimates were 66% for group 1, 95% for group 2, and 100% for group 3. There was a suggestion that the risk of rejection was different between the 3 groups ($p = 0.06$) and the 3-year estimates of graft rejection were 22%, 32%, and 12%, respectively. The estimated probabilities of grades III-IV acute GVHD were 15% for group 1, 0% for group 2, and 3% for group 3. The 2-year estimates of chronic GVHD were 21%, 21%, and 7%, respectively. In summary, advances in conditioning and GVHD prophylaxis regimens as well as supportive care during the past 39 years have led to improved outcomes for pediatric patients with severe aplastic anemia. These results strongly support the use of allogeneic marrow transplantation for newly diagnosed pediatric patients with severe aplastic anemia who have an HLA-matched related donor.

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HIGH DOSE ORAL BUSULFAN AND INTRAVENOUS MELPHALAN AS CONDITIONING THERAPY FOR AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) FOR THE TREATMENT OF PEDIATRIC SOLID TUMORS

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Disseminated or relapsed pediatric solid tumors usually have dismal prognosis and HSCT has been used as a treatment option for children with chemo-sensitive tumors. With modern intensive protocols, patients usually have been treated with many different drugs and may have some degree of renal or cardiac compromise. One interesting alternative would be to use two alkylating agents, busulfan and melphalan: these drugs are not used in pediatric chemotherapy protocols, their most important dose-limiting toxicity is marrow suppression, and they are not toxic to the heart or kidneys. Our objective is to describe the institutional experience with autologous HSCT with busulfan-melphalan for the treatment of relapsed or disseminated pediatric solid tumors.

Results: Nineteen patients with a median age of 11 years (2-33), 10 male, were transplanted, 12/19 with measurable disease. Diagnoses were alveolar sarcoma (1), desmoplastic small round cell tumor (DSRCT, 1), Wilms tumor (1), primitive neuroectodermal tumor (PNET, 2), synovial sarcoma (2), Ewing sarcoma (6, all but 1 with advanced disease), and stage-4 neuroblastoma (6, only 1 in 1st remission). All patients had normal marrow aspirate and biopsy prior to transplant, including immunocytochemistry. Conditioning therapy was busulfan 1 mg/kg/dose q 6 hours PO for 4 days on D-5 to D-2 and melphalan 140 mg/m^2 IV on D-1. Local irradiation, when planned, was postponed for the post transplant period. Three received bone marrow grafts and 16 peripheral blood stem cells with target cell dose of $5x10^6$ CD34 cells/kg. All patients engrafted promptly and none of them had severe toxicities. One had late sinusoidal obstruction syndrome and one Ewing sarcoma patient had Guillain Barre Syndrome at the time of post HSCT irradiation to his leg. One patient with PNET, the patient with DSRCT, Wilms tumor and 3/6 with Ewing sarcoma died of their primary disease after a median of 320 days post HSCT. The patient with alveolar sarcoma, both with synovial sarcoma, 3 with Ewing sarcoma and all neuroblastoma patients remain in remission and well after a median of 10.5 months post transplant (2-119). In conclusion, busulfan-melphalan was very well tolerated and 13/19 patients with advanced tumors remain well and in remission. Longer follow up and a larger number of patients are needed to define the – promising – role of this preparative regime for high dose chemotherapy and HSCT in the treatment of relapsed or disseminated solid tumors.

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INCIDENCE OF SECOND MALIGNANCIES (SMN) IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) RECIPIENTS: A REPORT COMPARING THOSE WITH AND WITHOUT EXOSTOSES

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Among 650 patients transplanted in our institution between 1992 and 2008, 19 (3%) are known to have developed a SMN post-HSCT. We have studied HSCT survivors who developed exostoses. We identified 27 patients with clinical and/or radiologic exostoses transplanted between 3/1992 and 12/2003. One patient with exostosis had co-existent malignancies and was treated elsewhere so was excluded from all analyses due to incomplete data and the possibility of a genetic cancer susceptibility. This group was compared to controls that were matched for gender, age within 3 years and on same side of puberty, malignancy/not and HSCT type. Our aim is to describe whether the exostosis patients have a higher risk for developing SMNs post-HSCT. There were 6/26 (23%) with SMNs in the exostosis group, 4/26 (15%) in the control group (McNemar p-value

	+ TBI	Focal radiation n (%)	Age at first HSCT	Time HSCT to SMN	A/C GvHD
	n (%)	SMN in field n (% with focal)	Mean (range)	Mean (range)	%
Cases with SMN (n=6)	5 (83%)	5 (83%) 2/5 (40%)	5.5y (0.5-9.1)	11.3y (6.6-16.1)	AGvHD 17% CGvHD 50%
Controls with SMN (n=4)	3 (75%)	2 (50%) 1/2 (50%)	4.9y (1.4-9.1)	9.0y (4.3-13.3)	AGvHD 75% CGvHD 25%

0.73). All patients underwent HSCT for malignancies and none who received a reduced intensity HSCT have developed a SMN to date. Of those with exostoses, 1 patient had received autologous HSCT and underwent allogeneic HSCT for myelodysplastic syndrome. The other SMNs in this group include thyroid papillary carcinoma, osteogenic sarcoma, GIST, PNET. 3 of 4 SMNs in the control group had received allogeneic HSCT and all 4 had thyroid papillary carcinoma. Matched data analysis showed that exostosis cases were less likely to have been treated with steroids for acute GVHD (McNemar test p = 0.022) but no differences existed in other clinical variables examined. However, cases were younger at HSCT (3.9 vs 6.3 yrs, paired t-test p = 0.004) and had longer F/U than controls (11.7 vs 8.8 yrs, p = 0.003). There was no difference in time from HSCT to SMN (or latest F/U) by Kaplan-Meier (cases = 14.9, control = 12.7 yrs, log rank p = 0.35). Among all 52 patients without considering exostosis, the age at HSCT was not different for those with SMN than without (p = 0.87). Descriptive analyses comparing SMN occurrence in exostosis cases and controls appears in the attached table. In conclusion, for occurrence of exostoses our study showed only acute GVHD to be different between the groups, and the likelihood of SMN was similar for cases and controls. Of the 10 SMNs, 50% were thyroid carcinomas, which are common after low dose radiation exposure to the thyroid. Of note, 43% of the other solid SMNs among this group occurred in the field of focal radiation for the primary tumor, highlighting the importance of high dose focal radiation as a SMN risk.

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REDUCED TOXICITY CONDITIONING (RTC) AND ALLOGENEIC STEM CELL TRANSPLANTATION (ALLOSCT) IN 100 CONSECUTIVE PEDIATRIC RECIPIENTS: VERY LOW INCIDENCE OF DAY 100 TRANSPLANT RELATED MORTALITY (TRM)

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Myeloablative AlloSCT is associated with 20-40% non-relapse mortality (NRM) in the first 100 days. NRM depends in large part on graft source, disease and disease status and possibly intensity of conditioning. RTC may decrease NRM but pediatric data are limited (Satwani/Cairo BBMT, 2005). We evaluated the feasibility and toxicity of RTC-AlloSCT in 100 consecutive children (median age 9.23±6.79 yrs) with malignant disease (50) or non-malignant disease (50) undergoing UCB (n = 51), MFD (n = 41), or MUD (n = 8) AlloSCT (89 average risk, 11 high risk). Regimens included Busulfan (6.4-8mg/kg) + Fludarabine (150-180mg/m^2) ± ATG (8mg/m^2) (n = 45); Cyclophosphamide (60mg/kg) + Fludarabine (150mg/m^2) ± ATG (8mg/m^2) (n = 20); and Busulfan (12.8-16mg/kg) + Fludarabine (150mg/m^2) + Alemtuzumab (54mg/m^2) (n = 35). Mean follow-up is 1277 ±1041 days. Time to neutrophil and platelet engraftment was 19 ±10 days and 35 ± 26.6 days, respectively. Donor chimerism on day 30, 100 and 365 was 86 ±27, 92.6 ±15.8 and 93±16, respectively. Cumulative incidence of aGVHD and cGVHD was 24.7%±4.8% and 18.6%±4.7%, respectively. Day 100 and 5 year NRM was 4.1%±2.01% and 15±3.9 %, respectively. Overall incidence of primary graft failure (PGF) was 16.5%±3.7%. Incidence of PGF with UCB was 33.3%±6.8% vs. 0% for MUD and MSD (p < 0.0001). Incidence of PGF with UCB in chemo-naive vs. non-chemo-naive patients was 48.3%± 9.3% vs. 10.5%±7 % (p < 0.0072). The 5 year probability of OS and EFS was 69%±5% and 56.4%±5.4%, respectively. On univariate analysis, age (p = 0.12), malignant disease (p = 0.1), UCB (p = 0.02), poor risk disease (p = 0.001), chemo-naive patients (p = 0.1), fungal infection (p = 0.01), alemtuzumab based RTC (p = 0.03) and PGF (p = 0.03) were associated with poor OS. However, on Cox proportional hazard model based multivariate analysis only graft failure (p = 0.028) and poor risk disease (p = 0.03) were associated with poor OS. In summary, in this largest reported pediatric series, RTC-AlloSCT demonstrated substantially reduced day 100 NRM and sustained donor chimerism. However, chemo-naive children undergoing RTC-AlloSCT with UCB grafts have a higher incidence of PGF, and poor OS.

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DACLIZUMAB AS A SECOND-LINE TREATMENT OF GI GRAFT-VERSUS-HOST DISEASE IN PEDIATRICS

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Background: Steroid-refractory acute gastrointestinal graft-versus-host disease (GvHD) remains major cause of mortality in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT). Among newly developed agents suitable for the treatment of GvHD, monoclonal antibodies hold much promise.

Methods: we report a series of 10 children who underwent allogeneic transplant from June 2007 through June 2009 and were treated with daclizumab for steroid-refractory acute GI GvHD (grade III-IV). Median of patients' age was 6.27 years (range 1-11) and 8 of patients were male. 8 of 10 patients underwent myeloablative and 2 of them nonmyeloablative stem cell transplant. Bone marrow (BM), peripheral blood (PB), and cord blood were stem cell sources in 4 patients, 3 patients and one patient respectively. Additionally, double cord blood in one patient and BM and PB concurrently in another one were used. Patients were transplanted from full match related (n = 6), one locus mismatch related (n = 1), two locus mismatch unrelated (n = 2) and haploidentical related (n = 1) donor because of Thalassemia (n = 4), Acute Lymphoblastic Leukemia (n = 2), Aplastic Anemia (n = 1), Fanconi Anemia (n = 1), Leukocyte Adhesion Deficiency (n = 1), and Wiskott-Aldrich Syndrome (n = 1). After first line therapy failed to control GvHD, Daclizumab added at a dose of 1 mg/kg every 10-14 days until response achieved and/or maximum 5 doses administered.

Results: 9 of 10 patients (90%) responded to Daclizumab therapy completely, but one patient failed. There were no infusion-related reactions. 8 patients developed CMV infection during Daclizumab therapy. Invasive fungal and bacterial infections occurred in 6 patients following Daclizumab therapy. Seizure and Guillain-Barre were important complications after daclizumab therapy in two patients which may be attributable to this monoclonal antibody. At a median follow-up of 460 days, 8 patients (80%) are alive and free of GvHD, severe infections and underlying disease. The remaining two patients died because of bacterial meningitis and severe non-responding acute GI GvHD. Limited Chronic GvHD, occurred in 2 patients.

Conclusions: Daclizumab was able to induce complete responses in pediatric patients with refractory acute gastrointestinal GvHD, but is associated with morbidity and mortality due to infectious complications. Aggressive prophylaxis against viral and fungal infections is recommended.

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A PROSPECTIVE STUDY OF REDUCED INTENSITY CONDITIONING (RIC) IN CHILDREN UNDERGOING UNRELATED UMBILICAL CORD BLOOD TRANSPLANTATION (UCBT) FOR NON-MALIGNANT DISEASES: PRELIMINARY RESULTS DEMONSTRATE A HIGH RATE OF ENGRAFTMENT AND LOW INCIDENCE OF GVHD

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Reduced intensity conditioning (RIC) reduces transplant related morbidity and mortality. However, engraftment remains a challenge after RIC in children with non-malignant disorders undergoing UCBT. We designed a novel RIC regimen for such children to study its efficacy to promote durable engraftment. Outcomes of 8 such children enrolled between Dec 2008 and July 2010 are presented in this preliminary analysis. RIC regimen consisted of alemtuzumab (3.2mg/kg), hydroxyurea (HU), fludarabine (FLU) 150 mg/m^2,